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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHOHEI KOIDE

Appeal 2011-012065
Application 09/903,412
Technology Center 1600

Before ERIC GRIMES, RICHARD M. LEBOVITZ, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a modified fibronectin type III molecule. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

Background

"Fibronectin is a large protein which plays essential roles in the formation of extracellular matrix and cell-cell interactions; it consists of many repeats of three types (I, II and III) of small domains" (Spec. 18, ll. 22-24). The Specification teaches that "Fn3 itself is the paradigm of a large subfamily (Fn3 family or s-type Ig family) of the immunoglobulin superfamily (IgSF). The Fn3 family includes cell adhesion molecules, cell surface hormone and cytokine receptors, chaperonins, and carbohydrate-binding domains" (Spec. 18, ll. 24-28).

The Claims

Claims 1, 4, 7, 8, 55-57, 59-64, 66-78, and 80-82 are on appeal. Claims 1 and 80 are representative and read as follows:

> 1. A modified human fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to the wild-type human Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a neutral or positively charged amino acid residue, wherein amino acid residue 6 is Arg.
>
> 80. A modified human fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to the wild-type human Fn3, wherein the stabilizing mutation is a substitution of Asp 7 or Asp 23 with a positively charged amino acid residue.

The issue

The Examiner rejected claims 1, 4, 7, 8, 55-57, 59-64, 66-78, and 80-82 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under §103(a) as being obvious over Lipovsek[1] (Ans. 4-9).

The Examiner first cites our decision in Appeal 2009-1912 (Ans. 4-9). The Examiner then finds that "given the homology among the mammalian Fn3 species shown in Fig. 4, the sequences differ in one or more amino acids e.g., positions 7, 9 or 23; and its known mimic of antibody substitution one can readily envisage the claim modified human FN3" (Ans. 16).

Appellant contends "while amino acid residue 6 of the HsFND, Rn and Bt sequences is Arg, Applicant submits that none of HsFND or Rn or Bt comprise a substitution of at least one of amino acid residues 7, 9 or 23 with a neutral or positively charged amino acid residue. Accordingly, Lipovsek does not anticipate the claimed invention" (App. Br. 10). Regarding claim 80, Appellant "submits that Asn is not a positively charged amino acid residue. Accordingly, Lipovsek does not anticipate the claimed invention" (*id.* at 11).

The issue with respect to these rejections is: Does the evidence of record support the Examiner's conclusion that Lipovsek teaches or suggests fibronectin type III proteins with an Arg 6 and one of the recited substitutions at the Asp 7, Asp 23 or Glu 9 positions?

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[1] Lipovsek et al., US 6,818,418 B1, issued Nov. 16, 2004.

Findings of Fact (FF)

1. Figure 4 of Lipovsek is reproduced below:

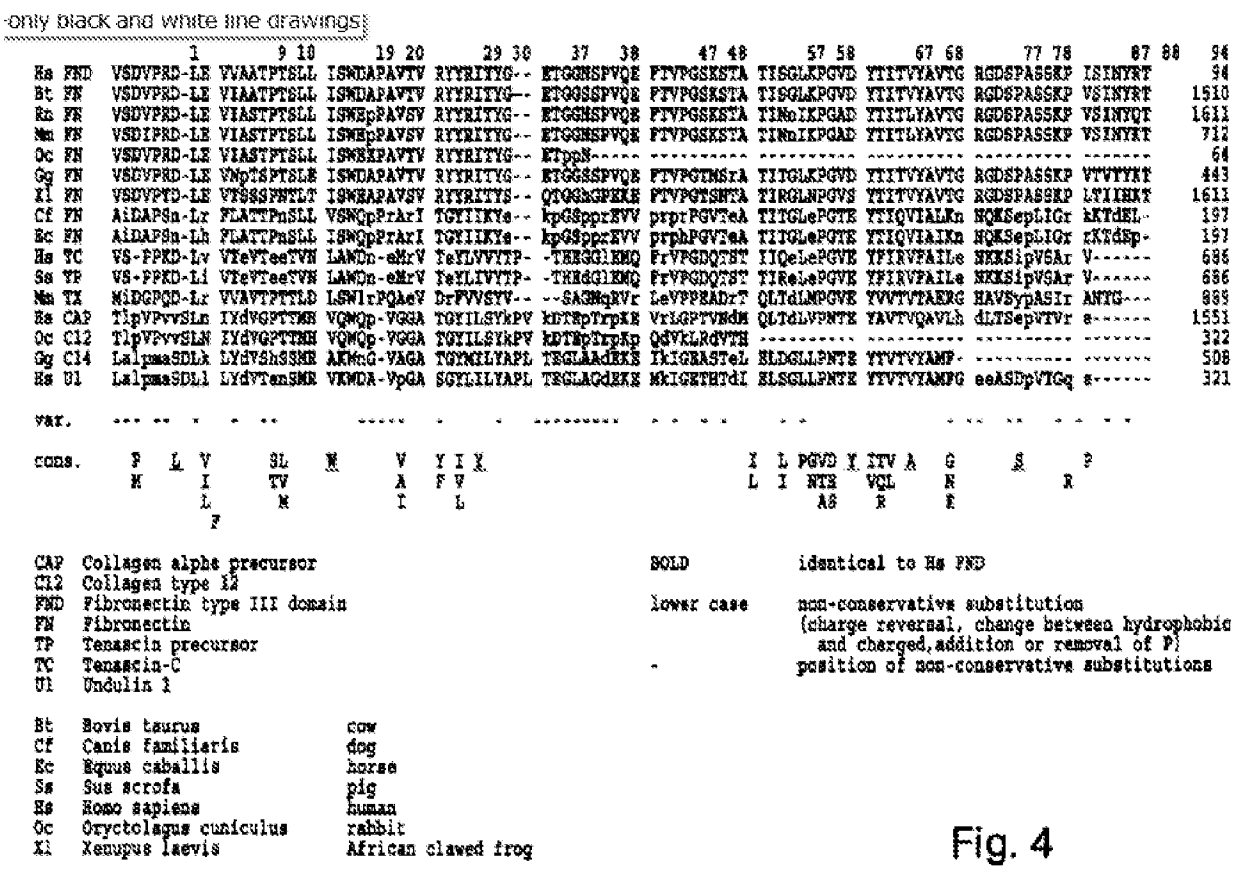

Fig. 4

"FIG. **4** is a graph illustrating a sequence alignment between a fibronectin type III protein domain and related protein domains" (Lipovsek, col. 6, ll. 31-33).

2. Lipovsek teaches "a protein that includes a fibronectin type III domain having at least one randomized loop" (Lipovsek, col. 2, ll. 32-34).

3. Lipovsek teaches that by "'naturally occurring fibronectin' is meant any fibronectin protein that is encoded by a living organism. By 'randomized' is meant including one or more amino acid alterations relative to a template sequence" (Lipovsek, col. 4, ll. 58-61).

4. Lipovsek teaches that the "three loops of ^{10}Fn3 corresponding to the antigen-binding loops of the IgG heavy chain run between amino acid residues 21-31, 51-56, and 76-88" (Lipovsek, col. 8, ll. 18-20).

5. Lipovsek teaches that for "the human ^{10}Fn3 sequence, this analysis indicates that, at a minimum, amino acids 1-9, 44-50, 61-54, 82-94 (edges of beta sheets); 19, 21, 30-46 (even), 79-65 (odd) (solvent-accessible faces of both beta sheets); 21-31, 51-56, 76-88 (CDR-like solvent-accessible loops); . . . may be randomized to evolve new or improved compound-binding proteins" (Lipovsek, col. 9, ll. 24-32).

6. Lipovsek teaches that "a fibronectin type III domain includes a sequence which exhibits at least 30% amino acid identity, and preferably at least 50% amino acid identity, to the sequence encoding the structure of the ^{10}Fn3 domain referred to as '1ttg'" (Lipovsek, col. 4, ll. 45-50).

Principles of Law

> To differentiate between proper and improper applications of "obvious to try," this court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under § 103. In the first class of cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Analysis

Lipovsek teaches randomly substituting amino acids in fibronectin type III polypeptides at a variety of positions within the peptide sequence (FF 2-6). Lipovsek teaches a variety of specific fibronectin type III polypeptides (FF 1).

We begin by noting that the claims have been amended relative to the claims presented in the previous Decision to require either that "amino acid residue 6 is Arg" (Claim 1) and "a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a neutral or positively charged amino acid residue" or "a substitution of Asp 7 or Asp 23 with a positively charged amino acid residue" (Claim 80). Figure 4 of Lipovsek does not disclose any fibronectin type III molecules where Asp 6 is Arg and one of Asp 7, Glu 9, or Asp 23 is substituted, relative to human Fn3, with a neutral or positively charged amino acid residue (FF 1). Figure 4 of Lipovsek also does not disclose any fibronectin type III molecules where amino acids Asp 7 or Asp 23 are substituted, relative to human Fn3, with a positively charged amino acid residue (FF 1). We also note that Asparagine is not a positively charged amino acid residue under the broadest reasonable interpretation rubric (*see* Ans. 23).

We therefore conclude that Lipovsek does not anticipate the instant claims.

With regard to obviousness, in *Kubin*, the court made clear that "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Kubin*, 561 F.3d at 1359. The obviousness rejection of these claims is such a situation, where the prior art gives an

immense number of possible mutations in the fibronectin type III molecule including more than 70 different amino acid positions which may be mutated, potentially to any of the other 19 amino acids not occurring at that position (*see* FF 5). Lipovsek does not provide any guidance on which parameters were critical and no direction on which of these mutations is likely to be successful in producing a stabilizing mutation (FF 1-6).

Unlike *Kubin*, where performing the detailed methodology of cloning would necessarily result in obtaining a molecule within the genus of nucleic acids being claimed, there is no predictable expectation that performing the random screening methods of Lipovsek would predictably, or even likely, result in polypeptides with one of the recited mutations at positions 7, 9 or 23 of the fibronectin type III molecule. Further, even if such polypeptides were obtained, there is no predictable or even minimally likely expectation that the mutations would result in stabilization of the fibronectin type III molecule.

The Examiner has not established, and we do not find, that the ordinary artisan would have predictably modified positions 7, 9 or 23 of the fibronectin type III protein in order to obtain a stabilizing mutation based on Lipovsek. The Examiner has provided no evidence that mutations at any of these three positions would have predictably or reasonably been expected to have this property, nor has the Examiner presented any other evidence to select any of these three positions from the 70 positions disclosed by Lipovsek as mutation targets (FF 5).

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Lipovsek teaches or suggests fibronectin type III proteins with an Arg 6 and substitutions at the Asp 7, Asp 23 or Glu 9 positions.

SUMMARY

In summary, we reverse the rejection of claims 1, 4, 7, 8, 55-57, 59-64, 66-78, and 80-82 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, 103(a) as being obvious over Lipovsek.

REVERSED

cdc